

# Risk factors of transient ischemic attack: An overview

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## ABSTRACT

Transient ischemic attack (TIA) is a transient episode of neurologic dysfunction caused due to loss of blood flow to the brain or spinal cord without acute infarction. Depending on the area of the brain involved, symptoms of TIA vary widely from patient to patient. Since the blockage period in TIA is very short-lived, there is no permanent damage. Risk factors for TIA include family history of stroke or TIA, age above 55 years or older, higher risk of TIA in males than females, high blood pressure, diabetes mellitus, and tobacco smoking. Genetics, race, and imbalance in lipid profile are other risk factors of TIA. TIA is usually diagnosed after taking a thorough history and a physical examination. Several radiological tests such as computed tomography and magnetic resonance imaging are useful in the evaluation of patients who have had a TIA. Ultrasound of the neck and an echocardiogram of the heart are other tests useful in the diagnosis and evaluation of the attack. The treatment following acute recovery from a TIA depends on the underlying cause. Patients who have more than 70% stenosis of the carotid artery, removal of atherosclerotic plaque is usually done by carotid endarterectomy surgery. One-third of the people with TIA can later have recurrent TIAs and one-third can have a stroke because of permanent nerve cell loss. Having a TIA is a risk factor for eventually having a stroke. Educating the patients and inculcating lifestyle modifications in them are initial steps to minimize the prevalence of transient ischemic attack.

**Key Words:** Radiological tests, risk factors, stroke, surgery, transient ischemic attack

## INTRODUCTION

Transient ischemic attack (TIA) is an acute episode of temporary neurologic dysfunction that typically lasts less than an hour; results from focal cerebral, spinal cord, or retinal ischemia, and is not associated with acute tissue infarction.<sup>[1]</sup> Whereas the classical definition of TIA included symptoms lasting as long as 24 h, advances in neuroimaging have suggested that many such cases represent minor strokes with resolved symptoms rather than true TIAs. Thus, the American Heart Association and the American Stroke Association (ASA) endorse a tissue-based definition of TIA (i.e., as an episode of focal

ischemia rather than acute infarction) rather than a time-based definition.<sup>[2]</sup>

TIAs are often neglected because symptoms tend to improve. Further interaction of medical individuals with the public is very necessary to improve this awareness.<sup>[3]</sup> In people who have a TIA, the incidence of subsequent stroke is as high as 11% over the next 7 days and 24-29% over the following 5 years.<sup>[4]</sup> There is a paucity of population-based data about the coexistent proportions of risk factors for stroke in South Asians. Therefore, this review is carried out to find out the risk factors and burden of TIA in India. Over the years, many researches done on different aspects of TIA have improved the understanding regarding definition and unveiled many

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new risk factors. The extent and diversity of vascular outcomes and evaluation techniques have changed the outlook to TIA. The aim of the review is to systematically review and analyze all the recent advances with respect to the mentioned entities.

## **BURDEN OF DISEASE**

Three transitions have contributed to the emergence of the stroke epidemic in India: Demographic, lifestyle, and socioeconomic.<sup>[5-7]</sup> Recent study identified that 7% of medical and 45% of neurological admissions were due to stroke with a fatality rate of 9% at hospital discharge and 20% at 28 days.<sup>[8]</sup> For India, the overall age-adjusted prevalence rate for stroke is estimated to lie between 84 and 262/100,000 in rural and between 334 and 424/100,000 in urban areas. Whereas in the US, TIAs are diagnosed annually between 200,000 and 500,000.<sup>[9,10]</sup>

TIA carries a particularly high short-term risk of stroke, and approximately 15% of diagnosed strokes are preceded by TIAs. Seven percentage to 40% of the stroke patients are found to have history suggestive of TIA episodes. The variability in the epidemiological data is attributed to disparities in TIA definition, stroke subtypes, evaluation on the basis of clinical examination and neuroradiological variabilities. The introduction of new tissue-based definition has led to a reduction in the incidence of TIAs by approximately 30% and a resultant 7% increase in the number of cases labeled as stroke. The higher incidence in elderly, males, and African-Americans contributes to heterogeneous distribution and thus variable results.

The major drawback is the inability to estimate true prevalence of TIA. The limited awareness about symptoms and severity of situation decreases the proportion of patients reporting to a health care provider. The situation is exacerbated by the differing epidemiological study criterion and inability of public and health care systems to recognize transitory focal neurological symptoms associated with TIAs.<sup>[11]</sup>

## **Urgency to understand the pitfalls**

One-third of the cases of ischemic stroke being preceded by TIA make the treatment an opportunity to decrease incidence of stroke. In patients of ischemic stroke with a preceding TIA, there has been a history of warning event in 26% of cases within a day.<sup>[11]</sup> Ten percent to 15% of patients are reported to have a stroke within 3 months, with half occurring within 48 h. Timely evaluation and diagnosis of ischemic stroke are paramount due to narrow therapeutic window. The pitfall of the situation is the inadequate awareness regarding the basic nature (only 26%

of women  $\geq 65$  years of age being well-informed about stroke, risk factors, signs, and symptoms (only 37% of women recognized weakness or numbness of the face or a limb as a warning sign of stroke, progression of disease, and the gravity of the situation for immediate treatment). The Indian study documents 23% of its participants to be ignorant about stroke warning symptoms and the rest responded to various warning symptoms.<sup>[12]</sup>

## **SEARCH STRATEGY**

A Medline search of the relevant publications and the references of the studies were incorporated to obtain the data. The search strategy used keywords as TIA crossed with terms, definitions, epidemiology, incidence, prevalence, etiology, risk factors, prognosis, recurrent stroke, and diagnosis. The search was limited from 1996 to 2014. Very old studies were not considered fit for the review.

## **Risk factors of transient ischemic attack**

There is a need to have precise knowledge of TIA risk factors to plan cost-effective and competent preventive strategies. According to current guidelines of the ASA, risk factors are classified in a evidence-based approach and with a flexible nature: Nonmodifiable (age, sex, race, and significant family history); well-documented and modifiable (tobacco smoking, obesity, physical inactivity, cardiovascular, and lipid profile derangements - coronary artery disease, myocardial infarction, valvular disease, atrial fibrillation, diabetes mellitus, arterial hypertension, and peripheral arterial disease); and potentially modifiable (history of migraine, obstructive sleep apnea, sleep patterns, and high-risk alcohol consumption).<sup>[13,14]</sup>

## **Nonmodifiable risk factors**

These factors reflect the high risk population and provide an opportunity to halt the progression of other modifiable risk factors present in them.

## **Age**

Age is the single most important and well-documented risk factor. The stroke rate is observed to double every 10 years after the age of 55.<sup>[15]</sup> Mortality rate of stroke is higher in women because although TIA incidence rates are 1.25 times greater in men, longevity of life in women contributes to the situation. The change in risk factor profiles with increasing age is the contributing factor to the trend. There is accumulation of associated risk factors with increasing age, further rising the risk.<sup>[13,15]</sup>

## **Gender differences**

Studies in various parts of the world have found differences between sexes in stroke incidence, prevalence, mortality,

and outcomes. A higher prevalence of stroke may exist among women aged 45-54 years compared with similarly aged men. This potential disparity could be due in part to inadequate stroke risk factor modification in women and requires further study.<sup>[16]</sup>

## **TRANSIENT ISCHEMIC ATTACK AND WOMEN**

One-third of strokes is said to occur among below the age of 65 years, but stroke in women is said to be an ongoing epidemic because of the sharp increase in stroke incidence with increasing age, the rapidly aging population, and the greater longevity of women as compared to men.<sup>[17]</sup> In women before menopause, stroke remains a potentially devastating occurrence during pregnancy and the postpartum period, especially in cases of multiple pregnancies and those with eclampsia.<sup>[18]</sup>

Postmenopausal hormone use has also been associated with a small but statistically significant increase in the risk of stroke in observational studies and randomized controlled trials such as the Women's Estrogen for Stroke Trial and the Women's Health Initiative.<sup>[19,20]</sup> The numerous studies devoted to oral contraceptives and stroke have shown that oral contraceptives containing a high content of estrogen increases the risk of stroke by 4 times whereas oral contraceptives with low estrogen content "only" doubles the risk of ischemic stroke.<sup>[21]</sup>

In addition, TIAs and migraines have both been found to increase the risk of ischemic strokes in women. The risk for ischemic strokes may be further increased in patients with both of these risk factors. The risk of ischemic stroke is lower following TIA in women with migraine history (compared with those without migraine) suggesting potentially different pathophysiology in such women.<sup>[22]</sup>

### **Genetic association**

An increased incidence of stroke in families has been known for long. It was observed that both paternal and maternal histories were associated with an increased risk of stroke.<sup>[13]</sup> There is a contrary view which claims that family history of stroke does not predict the risk of ischemic stroke after TIA.<sup>[23]</sup> Another genetic trait recognized was MTHFR 677T allele, suggested to be a genetic stroke risk factor and indicating a causal relationship between elevated homocysteine and stroke.<sup>[24]</sup>

### **Race and ethnicity**

There is extensive racial and ethnic diversity found in TIA prevalence and stroke mortality. The incidence of TIA has been observed to be significantly high in rural areas as compared to urban population.<sup>[25]</sup> The greatest incidence of TIA has been observed in black men  $\geq 85$

of age more common in Mexican Americans compared with nonhispanic whites with difference growing with increasing age.<sup>[26,27]</sup>

### **Modifiable risk factors**

#### ***Lifestyle risk factors***

Obesity, smoking, alcohol consumption, diet, drug abuse, and physical inactivity were each identified as modifiable lifestyle risk factors for stroke. Obesity has been identified as the independent risk factor and also in the context of increased incidence of associated derangements.<sup>[28]</sup> Drug abuse including cocaine, heroin, amphetamines, lysergic acid diethylamide, phencyclidine, and marijuana has been evident to increase the incidence of ischemic stroke.<sup>[29]</sup> Sleep pattern have been implicated as potential risk factor mostly in the young men with short sleeping span.<sup>[30]</sup> Another aspect is daytime napping migraine with aura and obstructive sleep apnea, which was more common in older patients.<sup>[31]</sup> Unhealthy lifestyle is associated not only with higher risk of subsequent stroke, but also with higher all-cause mortality after stroke.<sup>[32-34]</sup> Interventional strategies such as avoidance of obesity, smoking, heavy alcohol consumption, unhealthy diet, and physical inactivity can significantly decrease the prevalence of TIA.<sup>[35]</sup>

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#### ***Potentially modifiable risk factors include hypertension, cardiovascular factors, lipid profile, and cerebral microbleeds***

Blood pressure (BP) is a major risk factor for TIA and ischemic stroke. There has been evidence regarding decrease in the recurrence rates on antihypertensive interventions. However, there are some pitfalls of the situation, one being the variability of systolic BP and diastolic BP, technical errors, and criteria for initiating the antihypertensives. Single measurements are not a reliable idea of BP and will substantially underestimate the true prevalence of hypertension. Atrial fibrillation has been known to increase the incidence of stroke, but no relation has been proved with TIA.<sup>[37]</sup> Furthermore, there is debate regarding the baseline BP criteria to start the intervention, but the trials have showed that the relative benefit from BP lowering was independent of baseline BP. It is highly effective in preventing stroke in both primary

prevention and after a TIA or stroke.<sup>[38,39]</sup> There has been no direct evidence regarding beneficial effects of statin therapy on incidence of TIA; however, it could indirectly reduce the risk of atherosclerotic disease, primary culprit in ischemic stroke. Cerebral microbleeds are attributed by hypertension and drugs preventing stroke. Microbleeds results in poor cognition and impaired motor function in ischemic stroke. It has been found to increase the severity of symptoms in TIA and stroke. Antecedent BP also contributes to the future risk of ischemic stroke. Optimal prevention of late-life stroke will likely require control of midlife BP [Table 1].<sup>[40]</sup>

**Risk factors: The present scenario**

Recent studies based on risk factors of TIAs have found out more risk factors than we have known for the TIA. Herpes zoster has been recognized as an independent risk factor for vascular diseases particularly for stroke, TIA, and myocardial infarction with affliction of patients below the age of 40 years.<sup>[41]</sup> The risk appears to be reduced in older patients due to timely interventions for other contributing vascular factors. Lower serum brain-derived neurotrophic factor and higher vascular endothelial growth factor concentrations have also been found to increase the risk of incident stroke/TIA with modification of risk status of clinical and subclinical vascular brain injury.<sup>[42]</sup> Implication of respiratory infections in being potential risk factors for TIA was suggested. Investigations to prove the association have revealed that influenza vaccination was associated with a 24% reduction in risk of stroke, but not TIA whereas pneumococcal vaccination produced no reductions rates in either case. This has important implications for potential benefits of influenza vaccine.<sup>[43]</sup> Patients with low Vitamin B12 plasma levels, compounded by low folate levels have been observed to have increased risk

of cerebral ischemia. This effect is thought to be partly contributed by elevations of homocysteine levels, but there have been conflicting ideas about it. There have been evidences regarding increased risk of TIA in women who smoke and have FVL mutation and men who have the FII G20210A mutation, but not in women in this age group.<sup>[44]</sup> There have been findings regarding increased FIX activity in cases of TIA and stroke.<sup>[45]</sup>

**CLINICAL EVALUATION**

The newer ABCD2 score developed provides a more durable prediction standard and incorporates elements from both prior scores (The California score - assess the high risk patients and the ABCD score - which predict short-term risk of stroke in patients presenting acutely after a TIA). Patients with TIA score points (indicated in parentheses) for each of the following factors:

- Age ≥60 years (1)
- BP ≥140/90 mm Hg on first evaluation (1)
- Clinical symptoms of focal weakness with the spell (2) or speech impairment without weakness (1)
- Duration ≥60 min (2) or 10-59 min (1)
- Diabetes (1).

Data suggest that the 2-day risk of stroke was 0% for scores of 0 or 1, 1.3% for 2 or 3, 4.1% for 4 or 5, and 8.1% for 6 or 7. It was thought that prolonged duration of TIA symptoms or ABCD2 score were associated with diffusion weighted brain imaging (DWI) abnormality, which subsequently results in an increased early risk of stroke. However, the concept was negated and revealed no relation among DWI abnormality, duration of symptom, and motor symptom.<sup>[46]</sup> Lp-PLA2 mass and activity appears to provide additional prognostic information beyond the ABCD2 clinical risk score alone,

**Table 1: Risk factors of stroke/TIA**

Risk factors	Prevalence of risk factors (%) (India)	OR (India)	OR (India)	OR (India)	OR (US)	OR (Taiwan)	PARP* (India)
Study	Shah 2005 Sreedharan <i>et al.</i> 2009	Bhattacharya <i>et al.</i> 2005	Zodpey <i>et al.</i> 2000	Lipsaka <i>et al.</i> <45 years	AHA	Teng-Yeow Tan <i>et al.</i> 2004	
Alcohol consumption	22.5		1.96		1.8	0.5	0.09
Smoking	59	3.92	1.11	7.8	1.9	2.3	
Obesity	10-49		1.91		1.75-2.37		
Heart disease	7	6.20	3.4		1.73	4.4	
High cholesterol	32		2.27	0.2 per SD increment	2.0		0.14
Hypertension	20-40	2.79	1.99	1.9 per SD increment	1.0-4.0	2.7	0.17
Diabetes	12	1.73	2.39		1.8	1.7	
Family history of stroke	8						
Past history of TIA	10-15		8.44				0.08

\*PARP: Population attributable risk proportion. TIA: Transient ischemic attack, OR: Odds ratio, AHA: American Heart Association, SD: Standard deviation

especially for patients classified as moderate-risk using the ABCD2 clinical risk score (score of 4-5) and also the ones in the highest risk ABCD2 category (scores of 6-7).<sup>[47]</sup>

Neuroradiology holds importance in cases of TIA. Data prove brain imaging and vascular imaging to be important predictors of high risk patients performed early after an acute TIA. As suggested by computed tomography (CT) data, patients are considered to be at high risk if there is evidence of new infarction after TIA (despite a lack of symptoms).<sup>[48]</sup> For prognosis, diffusion weighted magnetic resonance imaging (MRI) is better as small volumes of ischemia could be missed on CT.<sup>[49,50]</sup> MRI has been confirmed to be superior in the context of triage of patients for admission, early after TIA. Vascular imaging including brain, carotid artery, and cardiac imaging are all frequently acquired for risk stratification.

## CONCLUSION

New data support the early interventions rather than delayed carotid endarterectomy for TIA patients with carotid stenosis. There have been conflicting ideas on the requirement of hospitalization, though the advantages include expedited diagnostic evaluation; timely thrombolytic management of deteriorating patients; early carotid revascularization; and risk factor modification.<sup>[51]</sup> The drawbacks include increased expenditure, incidence of deep venous thrombosis, and multiple infections. The end point relies on the risk stratification which decides the individual variability. Because of the narrow therapeutic window of the situation, it becomes mandatory to identify high-risk patients and optimizing management in individual centers. The challenges in this setting include diagnostic accuracy and resource availability, including both expert clinical opinion and modern imaging facilities. The drawback of the situation is the imperfect assessment despite the development of clinical risk prediction scores.<sup>[52]</sup>

Despite program efforts in public education, many patients still do not seek medical attention after experiencing TIA symptoms. A 2010 population-based study found that 31% of all patients who experienced a recurrent stroke within 90 days of their first TIA or minor stroke had not sought medical attention after the initial event.<sup>[53]</sup>

Public health professionals and physicians need to do more, such as promoting and participating in medical screening fairs and public outreach programs. In addition, patients need to be educated about lifestyle modification and cardiovascular risk factors.

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## Conflicts of interest

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